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Modulation of Strawberry/Cranberry Phenolic Compounds Glucuronidation by Co-Supplementation with Onion: Characterization of Phenolic Metabolites in Rat Plasma Using an Optimized μSPE−UHPLC-MS/MS Method

Stéphanie Dudonné,[†,‡] Pascal Dubé,[†,‡] Geneviève Pilon,[†,§] André Marette,[†,§] Hélène Jacques,[†,∥] John Weisnagel,[¶] and Yves Desjardins*[,†,‡]

[†]Institute of Nutrition and Functional Foods (INAF), Laval University, 2440 Boulevard Hochelaga, Québec (QC) G1V 0A6, Canada

[‡]Research Center of Horticulture (CRH), Laval University, 2480 Boulevard Hochelaga, Québec (QC) G1V 0A6, Canada

[§]Department of Medicine, Quebec Heart and Lung Institute (CRIUCPQ), Laval University, 2725 Chemin Ste-Foy, Québec (QC) G1V 4G5, Canada

[∥]Department of Food and Nutrition Sciences, Laval University, 2425 Rue de l'Agriculture, Québec (QC) G1V 0A6, Canada

[¶]Laval University Hospital Center (CHUL), Department of medicine, 2705 Boulevard Laurier, Québec (QC) G1V 4G2, Canada

Supporting Information

ABSTRACT: Plant phenolic compounds are suggested to exert pharmacological activities in regards to obesity and type-2 diabetes, but their mode of action is poorly understood due to a lack of information about their bioavailability. This work aimed to study the bioavailability of GlucoPhenol phenolic compounds, a strawberry−cranberry extracts blend, by characterizing plasma phenolic profile in obese rats. A comparison was performed by co-supplementation with an onion extract. Using an optimized μSPE−UHPLC-MS/MS method, 21 phenolic metabolites were characterized, mostly conjugated metabolites and microbial degradation products of the native phenolic compounds. Their kinetic profiles revealed either an intestinal or hepatic formation. Among identified metabolites, isorhamnetin glucuronide sulfate was found in greater amount in plasma. Three glucuronidated conjugates of strawberry−cranberry phenolic compounds, *p*-hydroxybenzoic acid glucuronide, catechins glucuronide, and methyl catechins glucuronide were found in higher quantities when GlucoPhenol was ingested together with onion extract (+252%, +279%, and +118% respectively), suggesting a possible induction of glucuronidation processes by quercetin. This work allowed the characterization of actual phenolic metabolites generated in vivo following a phenolic intake, the analysis of their kinetics and suggested a possible synergistic activity of phenolic compounds for improving bioavailability.

KEYWORDS: *bioavailability, GlucoPhenol, μSPE, phenolic metabolites, UHPLC-MS/MS*

INTRODUCTION

In recent years, phenolic compounds have been reported to possess various pharmacological actions, including antiobesity and antidiabetic actions.[1] These compounds exert their effects through different mechanisms such as the reduction of oxidative stress and inflammatory processes, the improvement of glucose and lipid metabolism as well as sensitivity to insulin.[1−3] Biological activities of phenolic compounds are known to be strongly dependent on their bioavailability, which is defined as the proportion of the nutrient that is digested, absorbed, and metabolized through normal pathways. Bioavailability differs greatly between the compounds, so that the ones most abundant in the diet are not necessarily those leading to the highest concentrations of metabolites circulating in the plasma. Moreover, the metabolites appearing in the circulation may not have the same bioactivity as that of parent compounds, often determined in vitro.

The general metabolism of phenolic compounds is rather well understood.[4,5] During food ingestion, phenolic compounds can be released from the food matrix by mastication and can be hydrolyzed in part by oral microbiota.[6] In the stomach, most of the phenolic compounds probably resist acid hydrolysis and arrive intact to the intestine, their major site of absorption.[7] Mostly present as esters, glycosides, or polymers, phenolic compounds are very poorly absorbed in their native form and must be hydrolyzed. Phenolic glycosides are deglycosylated in the lumen by membrane-bound lactase-phlorhizin-hydrolase (LPH), and the released aglycones enter the epithelial cells by passive diffusion as a result of an increased lipophilicity.[8] The phenolic glycosides may also be deglycosylated in epithelial cells by cytosolic β-glucosidase after they have been transported through the epithelium by sugar transporters such as SGLT1 (sodium-dependent glucose transporter).[9] Once absorbed, the phenolic aglycones undergo methylation, glucuronidation, and sulfation.[10] This conjugation process, which occurs mainly in liver, represents a metabolic detoxification process, which aims to facilitate the excretion of phenolic compounds by increasing their

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